ART. VIII.—*Cases of Splenic Leukæmia, and their Treatment with Hypodermic Injections of Ergotine; with Remarks on the Hypodermic Use of Ergot and of Iodine in Glandular Enlargements.* By J. M. DA COSTA, M.D., Professor of Practice of Medicine in the Jefferson Medical College, Philadelphia; Physician to the Pennsylvania Hospital.

I PURPOSE in this paper to place on record some cases of splenic leukæmia, and especially to comment on the treatment employed. But let the cases speak for themselves.

CASE I. Emma S., 25 years of age, single, was admitted into the Pennsylvania Hospital on the 16th of March, 1874, and sent to my ward. A sickly looking, pale creature, of inordinate appetite, yet constantly wasting, she was brought to the hospital to be treated for what the family conclave had determined to be a tapeworm. Partly from some relatives who accompanied her, partly from herself, we learned that she had not for years been in strong health. Her menstruation began at the age of sixteen, and had never been regular, the intervals at times being as long as six months, and the discharge nearly always scanty. Her last monthly sickness, occurring not long since, and also happening after six months' intermission, was, however, exceptionally profuse. Much of her debility was attributed to an attack of "slow fever," presumably typhoid, which she had at the age of thirteen.

Yet, notwithstanding her delicate health, she was not regarded as being really ill until early in the spring of 1873, when she began to complain often of a heavy pressure on the top of the head and the upper portion of the spine, and when the inordinate appetite already alluded to began to attract attention. She was not actually hungry, nor did food taste well to her; but she was never satisfied. A dozen oranges at a time served but as a prelude to the consumption of enormous quantities of bread, and meat, and apples, and, in truth, of anything that was placed before her. But she rather lost than gained flesh, nor did her blood seem to improve, for ecchymotic spots were seen at various parts of the body—a reappearance rather than an appearance—for two years ago they had for a short time been noticed on the thighs and pelvis. Excepting obstinate constipation and dark offensive stools, there were none of the usual symptoms of digestive disorder until in August, when nausea and vomiting of starch-like matter occurred. About a month before she became conscious of a weight in the left side, and of a heavy mass which seemed to move about as she walked. During the past winter she was troubled with a severe cough, and she became very irritable; in some of her cross moods tearing everything she could get hold of, even her own clothing.

Several notes, taken shortly after her admission to the hospital, speak of her peculiar sallow and unhealthy aspect, of the anæmic looking gums and tongue, of the ecchymotic spots on the thigh, to the touch kernel-like under the skin, of her great debility and ravenous appetite. The temperature was rather low, a common record being 98° in the morning, with a pulse of 96, and respiration 24, and the same or a rise of half a degree in the evening, with sometimes a decrease in the pulse of ten beats; while 97° is also mentioned as the result of the morning observation. The urine was of specific gravity of 1020; on standing, an abundant deposit formed, consisting of amorphous urates and a few epithelial cells. The stools were mostly dark and hard; some, however, of mushy consistence, and contained a few particles of undigested food. The tongue was generally slightly coated with a moist, whitish fur. There were no special thoracic symptoms; the first sound of the heart was shorter than normal.

The chief signs of disease were found in the abdominal cavity. The large and flaccid abdomen was, as regards percussion, divided longitudinally into two almost equal parts, one everywhere dull, the other yielding a ringing tympanitic sound. Ascertained with accuracy, the line of decided dulness was found to begin in the sixth interspace anteriorly, and to extend into the axilla, curving then backwards and downwards; everywhere on the left side the dulness was marked, until on a line with the crest of the ilium it gave way to a tympanitic sound. In front the dulness extended to the median line, and on a level with the umbilicus crossed for two inches to the right. But a little lower down it passed back again to the left; on a level with the centre of the tumour the dulness did not go decidedly beyond the line of the axilla, where the sound became tympanitic. In truth, it was evident that the enlarged spleen, for such the swelling was recognized to be, was displaced, and occupied a slanting position. On palpation, its rounded edges could be felt, a notch be made out, and the organ be moved without occasioning pain or exhibiting tenderness, unless it were very much pressed out of the position it occupied, when pain was complained of. No increased percussion dulness in the hepatic region was discernible.

From no belief in the existence of a tapeworm, but partly to satisfy the patient's mind, partly also to see if brisk purgation would influence the extraordinary appetite and the digestive symptoms, she was placed on turpentine, followed by a few doses of male fern, and active cathartics. These remedies acted with difficulty on the sluggish bowels, but failed so utterly in yielding the least evidence of a parasite that even the patient became convinced It was, in truth, very obvious that the tumour was the cause of the malady, and this was diagnosticated before the clinical class at the hospital to be a non-malignant tumour of the spleen, of the nature of a general hypertrophy of the organ. The opinion advanced suggested, of course, a careful search for enlarged glands and swollen lymphatics all over the body, as well as an accurate examination of the blood. As regards the former inquiry, it gave negative results; the examination of the blood showed us, however, that we were dealing with a very remarkable case of splenic leukæmia. I subjoin the careful report of our microscopist, Dr. Jos. G. Richardson:—

> On examining a drop of fresh blood drawn about fifteen minutes after dinner from the patient, with enormously enlarged spleen, in the south ward of the Pennsylvania Hospital, I found the number of white blood-corpuscles much increased, and, to determine the relative amount of this increment, I resorted to the method (in part) of Vierordt and Welcker.
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> A small drop of blood, drawn by a needle puncture from the ball of the woman's middle finger, was received upon a slide, and then with the side of the needle gently spread out upon the glass so thinly as to afford portions where the film was of such tenuity as to consist of only a single layer of corpuscles, which almost immediately dried *in situ* upon the glass. The specimen thus prepared was then arranged beneath the microscope, in the field of a $\frac{1}{4}$ inch objective, and after replacing the ordinary *eye piece* by one containing a cobweb micrometer, with its threads adjusted so as to include a band $\frac{2}{1000}$ of an inch wide, across the field of view, I proceeded to count the red and white cells, comprised within this space, at five different places upon the slide.

The enumeration resulted as follows:—

Observation		Red corpuscles		Leucocytes	
Observation	1st	Red corpuscles	68	Leucocytes	60
"	2d	" "	119	"	59
"	3d	" "	126	"	34
"	4th	" "	88	"	53
"	5th	" "	128	"	54
	Total		529		260

I therefore conclude, that the case is one of very marked leucocythemia, in which the white blood-corpuscles bear to the red disks a proportion of about 1:2 instead of 1:357, the ratio asserted by Moleschott to exist in normal blood.

Here then we had a case of pure splenic leukæmia with extraordinary alteration of the blood; and the question arose, could we, while attempting to improve the character of the blood, do anything to reduce the enormous enlargement of the spleen? Iron, nitromuriatic acid, quinia, pepsin, carefully regulated food, seemed to have but little effect in fulfilling either indication, though there was a slight increase in general strength. Reflecting over the matter, I determined to try ergot hypodermically, and with this view began, March 24th, to inject from five to ten grains of ergotin into the abdominal covering chiefly, though also into the arms, very nearly every second day. The exact formula, and the one which was found to be the best suited, was forty grains of ergotine carefully mixed with thirty minims of glycerine, and enough distilled water added to make one hundred and twenty minims; fifteen minims of this would represent five grains, and was the average dose employed, though it was subsequently increased to twenty-five and thirty minims. By April 7th, the most marked diminution had taken place in the size of the tumour, but, as the arms were beginning to be sore from the repeated punctures, the injections were only made into the abdominal walls. As internal treatment she took for a time still nitromuriatic acid, varied by the administration of metallic iron.

By the 11th of the month the splenic tumour was so far reduced that it measured a full inch less in all directions, and the abdomen was less in circumference by several inches. But the patient began to complain of the pain of the injections, and had not gained in strength. The ergotine was now discontinued, and shortly afterwards a quarter of a grain of iodine, dissolved in twelve minims of glycerine and water, was employed hypodermically for five or six days, a further, though not so striking, reduction of the tumour taking place. Yet there was no improvement in her general condition; indeed, she spoke of being fainter, having pain in her head, her hearing had become much impaired, her eyesight was dimmed, and, though the extraordinary appetite remained, she was becoming thinner and paler day by day. Severe pain and tenderness on the left side of the abdomen were complained of, and these signs of a local peritonitis, which showed themselves for about eleven days before death, were preceded by a rise of temperature to 99° and then to 100°, the pulse being 82, at which both remained until very near to the fatal termination. All treatment, excepting the use of blisters and morphia, chiefly hypodermically, had been abandoned, and even with this it was difficult to control the severe pain, which she often likened to a feeling as if she would burst. She died on the 30th of April, completely exhausted.

Here is the record of the *post-mortem examination* made by our hospital pathologist, Dr. Morris Longstreth, twenty-four hours after death: Body extremely emaciated; no enlarged lymphatic glands to be found on any part of the surface of the body. Abdomen uniformly distended, firm and doughy under pressure, and not tympanitic. Rigor mortis firmly established. The abdomen was opened first. The subcutaneous fat had disappeared from the cellular tissue—the muscular walls were quite thin. Parietal peritoneum adherent to the omentum—especially marked on the left side. Sac of the peritoneum filled with blood, not clotted, and of a chocolate colour. *Spleen* reached across the abdomen somewhat to the right of the median line, and downwards about to the umbilicus. It also pressed up the diaphragm, the upper end reaching to the level of the third interspace, just above the left nipple. The organ was found inclosed in a loosish capsule of inflammatory lymph, which was traversed by numerous venous trunks about the size of a crow's quill. Its surface was somewhat roughened with inflammatory bands of lymph. Spleen measured in length 13½ inches, in breadth 6½ inches, in thickness 4 inches, weight 4 pounds 14 ounces avoirdupois. The vessels entering the hilus were very divergent and considerably enlarged. Tissue of the organ quite firm, trabeculæ thickened and prominent—the intratrabecular portions of the same colour as the blood found in the abdominal cavity. A little fluid blood escaped on section. *Stomach* distended with gas, it contained a small amount of fluid. Its mucous membrane normal in appearance, only slight evidences of post-mortem change of its surface being present. *Liver* increased in size, though not markedly so in its general aspect; outline regular; borders sharp; right lobe was rather prominent and thickened in the centre, taking the form commonly seen in compressed waists. On section, its tissue appeared uniform and normal, though congested and of a colour approaching that of the blood. Under surface covered with long shaggy bands of lymph which bound it to the omentum; upper surface smooth and not adherent to the diaphragm. Its weight was 6 pounds 14 ounces avoirdupois. *Gall-bladder* contained considerable green-coloured bile. *Kidneys* slightly enlarged; outline regular; capsule somewhat thickened and opaque, but not too adherent; the surface of the organ after the removal was smooth. On section, the cortical portion was found relatively enlarged. Their combined weight was 12 ounces. *Supra-renal capsules* healthy. *Omentum* greatly thickened, and adherent to the parietes of the abdomen, as well as to the liver, slightly to the intestines, and very firmly around the spleen. The substance of its mass was traversed by numerous large vessels—some of them larger than a goose's quill—and by an innumerable number of small vessels. The blood in the abdominal cavity had its origin apparently from the rupture of some of these vessels, although the exact seat of the hemorrhage could not be determined. *Intestines* somewhat matted together by lymph, but this was neither general nor marked, and seemed of recent date. Their adhesion to the omentum was of the same character and extent. Glands of the *mesentery* normal. *Reproductive system* apparently in a healthy condition. *Thorax—Pericardium* contained a small amount of fluid; the sac appeared in every respect normal. *Heart* of normal size; its weight, after being emptied of blood, 10 ounces avoirdupois; its cavities were distended with soft clots, without firmness and of a chocolate colour. The clots were continued into the great vessels and retained the same characters in those situations. When removed and placed on a plate, the blood-masses did not become diffluent, but flattened out, still preserving the smooth surface as moulded against the walls of the cavities and the vessels. *Valves* and the texture of the *muscular* *walls* appeared normal. *Pleural sacs* and *lungs* normal; hypostatic congestion not marked, and its colour partook of the chocolate tinge. *Left lung* considerably compressed by the upward protrusion of the spleen, and its lower border for about two inches in extent exhibited a condition of atelectasis from pressure (collapse). *Internal glandular system* wholly free from any enlargement and apparently normal. *Blood* throughout the body of a pretty uniform chocolate colour; no firm clots were to be found, certainly no trace of anything approaching a fibrinous mass. Under the *microscope*, the number of white corpuscles was seen to be enormously increased; the average of numerous specimens in which an actual count was made, showed the proportion of the white to the red corpuscles to be about as 2 : 3. *Muscular fibre of the heart* under the microscope, exhibited perfectly normal characteristics. Sections of the *liver* under the microscope showed doubtful appearances of what is described as "leukæmic swelling." The condition was not marked and was difficult of demonstration in any degree. There were no traces of a similar condition in the *kidneys*. The microscopic examination of the *spleen* showed a condition of *hypertrophy of all its elements*, as noted in its general description above. It was extremely difficult to make a satisfactory section even after hardening—the soft pulp escaping under pressure of the knife. No examination was made of the brain.

In reviewing the marked features of this striking case, attention is forcibly arrested by several points. In the proportion of the white to the red globules, it is one of the most remarkable on record; and the absence of any other glandular enlargement stamps it as one of the purest instances of splenic leukæmia. The temperature record is normal or but little altered, and for the most part below the healthy standard, excepting during the last thirteen days, when it rose to 99 and 100°, synchronously with the severe abdominal pain, due, I believe, to the peritonitis. But the rise may have been owing to the disease. In the second case to be reported the temperature was higher than normal, and in the only other observation that I can find anywhere on the temperature of leukæmia, that by Uhle, a steady increase of one to one and a half degrees was noticed during the latter weeks of life. It is thus a question whether the changed animal heat is due to the malady or to some complication. In the anæmia, the exhaustion, the quickened respiration, the wasting, the case presents nothing different from the usual course; but on the other hand the deafness, and the extraordinary appetite with progressive emaciation, suggest numerous interesting physiological and clinical inquiries. What became of all the food? The appearance of the stools showed, for the most part, that it was digested, yet it did not become converted into healthy blood, and the tissues continued to starve and to waste.

But to me the most interesting part was the evident reduction of the spleen by hypodermic injections. Those of iodine had some effect; but as they were tried about the beginning of the severe abdominal pain, and not long persevered in, I shall not dwell on their effect. Those of ergotine were, unquestionably, decided in their action; the splenic dulness on percussion, and the outlines by palpation—the skin being stained with nitrate of silver so as to preserve careful measurements—clearly proved this. True, the injections were attended with some inconvenience, and did not save the patient, because the blood had been already too profoundly altered, yet sufficient result was produced to show that earlier employed the chances of their acting favourably would have been very great. In a few well-observed cases which, Niemeyer tells us, throw a very clear light on the dependence of the dyscrasia on the disease of the spleen and lymphatic glands, it was found that the enlargement of the spleen and glands existed for months and years before the disorder of the blood manifested itself. Now it is here, I thought on reflecting over the results obtained in my patient, that the treatment employed would be likely to prove valuable. And I was able, not long since, to witness the good effects in a case which presented itself at the Jefferson Medical College Clinic.

Briefly told, it is this:—

Case II. Michael C., age 32, shoemaker, came to the clinic, October 12th, complaining of pain and a lump in the left side, both of fifteen months' duration. He looked pale, anæmic, and dejected. The tongue was slightly coated; there were symptoms of indigestion, and he was subject to frequent attacks of diarrhœa, alternating with constipation. The pain was only occasional in its appearance, and was described as not so much a pain as a dull feeling and a weight.

An examination of the thoracic and abdominal regions showed some prominence of the chest, on the left side, in its lower portion. The lungs were normal. Considerable beating of the heart was visible, but no murmur was heard, nor was there an increase in the extent of cardiac dulness; the first sound was a little more forcible than usual. Percussion of the splenic region gave a dulness extending from a point in the sixth intercostal space, two inches below the nipple, in a line with the front margin of the axilla, to a distance somewhat below the ribs—in all, a vertical diameter of six inches.

There was no enlargement of the liver, no dropsy, no lymphatic swellings. The patient suffered, besides the feeling of weight, with palpitation of the heart upon excitement, an occasional cough, and some oppression in breathing. The respirations were 20, the pulse was 72. An examination of the urine for sugar and albumen gave negative results. The microscopical examination of the blood showed in two yields, respectively, eighteen and twenty white corpuscles, in comparison with twelve and fourteen, respectively, of normal blood.

Careful inquiry into the patient's history was made; he, himself, attributed his trouble to overwork; he had never had a malarial attack.

A diagnosis of splenic enlargement with beginning leukæmia was evident, and led to the following treatment being directed: A hypodermic injection, on alternate days, of ergotine gr. v, in glycerine and water; also internally tinct. of choride of iron xx drops thrice daily.

The first injection was of one grain of ergotine, but the subsequent applications were of the strength prescribed above. The first two injections were made over the splenic region, the third injection and all the other ones were into the subcutaneous tissue of the left arm. On October 16th, after two injections had been made, the patient said that he felt better, and the splenic diameters were found to be less. An observation on the 20th, after five injections, records that the pupils are not dilated by ergotine, that there are no ulcers at former points of insertion, but, in each case, a trifling circumscribed slough of the skin. The temperature before the injection was 100.3°; after, the same. The temperature on several occasions showed a slight rise after the injection, but not of more than half a degree. October 21st, after six injections, the patient enthusiastically volunteered the information, that he felt splendidly, and the size of the spleen was observed to have much diminished. October 22d, after seven injections, the spleen was percussed, and found not extending to the lower rim of the ribs; very marked improvement in the patient's appearance was manifest, and he said that he had not felt so well for a year. October 29th, after eight injections, the colour of the face, lips, and tongue was almost normal; the appetite had greatly improved; the pain in the left side was gone. A microscopical examination of the blood, made by the first clinical assistant, Dr. James Wilson, showed the relative number of the white corpuscles to have become nearly normal, being 14 in the patient's case. as compared with 12 in the blood of a perfectly healthy person. Percussion of spleen gave a dulness of only $3\frac{3}{4}$ inches in the vertical diameter; the transverse diameter beginning on a line with the middle of the axilla. The temperature was normal. The patient was now dismissed as cured after being enjoined to continue the use of the iron.

I shall not comment any further on the features of this case than to call attention to the success of the treatment employed. That it would prove of much use in cases of large new formations in glands, malignant or non-malignant, I do not believe. But the majority of instances of glandular enlargement consist rather of a hypertrophy with considerable vascular increase, and here the treatment proposed is likely to do good. Nor is its application to be limited to cases of splenic disorder. As regards iodine, there is no reason why we should not try it in many instances of tissue change in organs, or their increase, for which iodine is indicated. I have so employed it, and have not found, keeping to the formula suggested, the least local trouble from its use. The patients sometimes speak of tasting the drug, and exhibit a passing swelling of the feet, which is not connected with albuminous urine. This was especially noticed in a case of most extensive goitre now under my observation, in which three hypodermic injections of iodine reduced the swelling in the neck half an inch in circumference. But as it is more my purpose here to speak of the hypodermic use of ergot, I must add that in the same case, three further injections of ergotine produced a like result of diminution, which is still going on under the treatment employed. And, on the whole, I think that this therapeutic plan is deserving of a careful trial in a number of cases of splenic and other glandular enlargements and alterations, for which our treatment hitherto has proved unsuccessful or of doubtful efficacy.